



Performance of the minimally invasive autopsy tool for cause of death determination in adult deaths from the Brazilian Amazon: an observational study

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Received: 1 April 2019 / Revised: 1 May 2019 / Accepted: 6 June 2019
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Abstract

The uncertainty about the real burden of causes of death (CoD) is increasingly recognized by the international health community as a critical limitation for prioritizing effective public health measures. The minimally invasive autopsy (MIA) has shown to be a satisfactory substitute of the complete diagnostic autopsy (CDA), the gold standard for CoD determination in low- and middle-income countries. However, more studies are needed to confirm its adequate performance in settings with different epidemiology. In this observational study, the CoD obtained with the MIA were compared with the clinical diagnosis and the results of the CDA in 61 deaths that occurred in an infectious diseases referral hospital in Manaus, Brazilian Amazon. Concordance between the categories of diseases obtained by the three methods was evaluated by the Kappa statistic. Additionally, we evaluated discrepancies between clinical and complete diagnostic autopsy diagnoses. The MIA showed a substantial concordance with the CDA (Kappa = 0.777, 95% CI 0.608–0.946), and a perfect or almost perfect coincidence in specific diagnosis (ICD-10 code) between MIA and CDA was observed in 85% of the cases. In contrast, the clinical diagnosis showed a fair concordance with the CDA (Kappa = 0.311, 95% CI 0.071–0.552). Major clinico-pathological discrepancies were identified in 49% of cases. In conclusion,

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Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00428-019-02602-z>) contains supplementary material, which is available to authorized users.

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the MIA showed a substantial performance for CoD identification. Clinico-pathological discrepancies remain high and justify the need for post-mortem studies, even in referral hospitals. The MIA is a robust substitute of the CDA for CoD surveillance and quality improvement of clinical practice in low- and middle-income settings.

Keywords Cause of death · Minimally invasive autopsy · Complete autopsy · Infectious diseases · Clinico-pathological discrepancies

Introduction

The uncertainty about the real burden of causes of death (CoD) is increasingly recognized by the international health community and the funding agencies as a critical limitation for prioritizing effective public health measures [1]. The complete diagnostic autopsy (CDA) is the gold standard to determine the CoD, but despite its benefits, the autopsy rates are declining worldwide [2–5]. The reasons are multiple and include the invasive nature of the procedure, which hampers its acceptability among next-of-kin and physicians, as well as the time spent by the pathologists and the high costs of the procedure [6, 7]. An additional reason is the perception of the clinicians that in this era of high-tech imaging exams and accurate laboratory tests, autopsies are no longer necessary [6]. However, major discrepancies between the clinical diagnosis and the final autopsy diagnosis are still relatively frequent [8, 9].

In high-income countries, imaging-based methods have been proposed as an alternative to the CDA, but the high costs and the high level of expertise required are major drawbacks for their implementation, particularly in low- and middle-income countries (LMIC). Moreover, these imaging-based methods could be insufficient for the identification of infectious CoD [10], presumably more frequent in LMIC. Therefore, innovative methods are necessary in LMIC, where most premature deaths occur, and robust mortality data are poor [1].

In recent years, the minimally invasive autopsy (MIA), a simple method based on needle sampling of fluids and key organs followed by histological and microbiological analyses, has been developed and validated in all age groups, including stillborn babies, neonates, children, and adults, including maternal deaths [11–14] in Mozambique. The concordance between the MIA and the CDA varies in the different age groups, ranging from moderate to substantial, and is particularly high for infectious diseases [11–14]. However, the MIA has only been tested in Mozambique and has not been evaluated in other LMIC with different epidemiological backgrounds. We hereby aimed to validate the MIA approach against the CDA and to assess the concordance between the clinical diagnoses and the CDA diagnoses in a series of deaths from an infectious diseases tertiary hospital in Manaus, Western Brazilian Amazon.

Materials and methods

Study setting and design

This observational study was conducted at the *Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* (FMT-HVD), a tertiary hospital, which is a national and international referral centre for the diagnosis and treatment of tropical diseases. The Institution is located in the municipality of Manaus, in the North East of the Amazonian State. The city has an estimated population of 2,094,301 inhabitants, of whom the majority reside in urban and peri-urban areas [15]. Major imaging exams and laboratory tests are fully available at FMT-HVD.

Deaths of any age having occurred within the hospital from March 2014 to February 2015 were eligible for recruitment. All patients had been referred to the FMT-HVD with the suspicion of infectious diseases. The inclusion criteria were as follows: (1) a CDA requested by the clinician as part of the medical evaluation of the patient, (2) written informed consent to perform the autopsy given by the relatives and (3) lapse of time between death and autopsy procedure of less than 48 h.

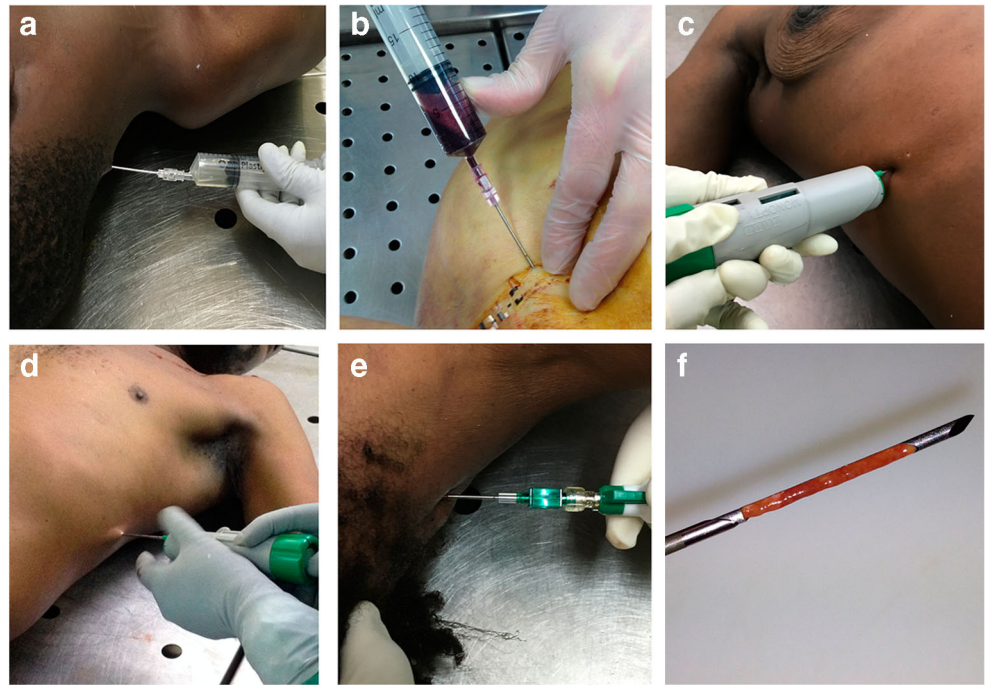
The study received the approval of the Clinical Research Ethics Committee of the Hospital Clinic of Barcelona (File 3024/9688) and the local (Manaus, Amazonas state) and National (Brazil) Bioethics Committees (CAAE 28905514.0.0000.0005/2014).

Autopsy procedures

The MIA procedure has been described in detail elsewhere [16]. The procedure included initial disinfection of the surface of the body followed by the collection of blood and cerebrospinal fluid (CSF), aiming to collect 20 mL of each fluid. It included the puncture of solid organs (liver, lungs and central nervous system [CNS]) using biopsy needles (14G–16G) and bone marrow (using a trephine needle) for microbiological and pathological analysis. In addition, the heart, spleen and kidneys were sampled for pathology examination. Representative figures of the sampling in a MIA procedure and an example of a lung core obtained during the procedure are shown in Fig. 1.

Immediately after the MIA, the CDA was conducted by a second pathologist not involved with the MIA and

Fig. 1 Representative figures of the sampling in a minimally invasive autopsy procedure. **a** Cerebrospinal fluid. **b** Peripheral blood. **c** Liver. **d** Lung. **e** Central nervous system biopsy. **f** Example of a lung core obtained during minimally invasive autopsy procedure



following a standardized protocol [17]. Histological and microbiological analyses were conducted in samples from the same viscera collected in the MIA and from any grossly identified lesions.

Histological and microbiological analyses

A team of two pathologists (P.C., J.O.) and two microbiologists (J.C.H., M.J.M.) analysed the MIA samples blindly to any clinical information. All the samples were stained with haematoxylin and eosin and ancillary histochemical and/or immunohistochemical stains if required. Microbiological methods have been reported in detail elsewhere [18]. In brief, universal screening was performed for all cases, which included detection of *Plasmodium falciparum* and *Plasmodium vivax* by PCR, detection of antibodies against HIV-1/2 and bacterial/fungal cultures of CSF, blood, lungs, liver and CNS.

Additional microbiological screening applied to all HIV-positive cases included real-time PCR in CSF and CNS samples for *Toxoplasma gondii*, *Mycobacterium tuberculosis*, and *Cryptococcus* spp. and in lung samples for *Pneumocystis jirovecii*, *Cryptococcus* spp. and *Mycobacterium tuberculosis*. Other microorganisms were tested depending on the histological findings of the MIA or the CDA (e.g. *Leishmania* spp., *Histoplasma capsulatum*) [19, 20].

The pathology team in Manaus (A.P., M.F., L.F.) analysed the CDA samples following the same approach used for the analysis of the MIA samples, with the only exception that CDA tissues were not routinely cultured.

Determination of the CoD

Once all the analyses of the MIA samples had been completed, a panel composed of a pathologist, a microbiologist and an internist evaluated all the data and assigned the MIA diagnosis. Details of the methodology for CoD determination have been described elsewhere [11]. Briefly, the MIA findings were used to assign the immediate condition leading to death. For the sake of the blind comparison MIA-CDA, no clinical information was used for the MIA diagnosis assignment, even if this could potentially result in a poorer concordance. A chain of conditions (up to four) was established following the most probable chronological sequence of events leading to death [21]. Fundamental diseases contributing to the death were classified as underlying conditions (e.g. HIV infection). In all cases, the immediate CoD and not the underlying disease was considered as the main CoD (e.g. disseminated histoplasmosis in an HIV-infected patient). Other conditions or concomitant infections unrelated to the chain of events were considered as other significant conditions.

The team from Manaus, which included three pathologists and an internist (A.P., M.F., L.F., M.L.), evaluated the data from the CDA and assigned the final CDA diagnosis using the same methodology. The CDA diagnosis integrated all the findings from the macroscopic, histological and microbiological analysis together with the clinical information and was considered the “gold standard” diagnosis.

All morbid conditions and any underlying diseases were codified following the International Classification of Diseases, tenth revision (ICD-10) [22], independently for the MIA and the CDA diagnoses. The CoD were classified into

four major categories: (1) infectious diseases, (2) malignant tumours, (3) other diseases (including non-infectious cardiovascular or pulmonary diseases) and (4) non-conclusive.

Review of the clinical charts

The available clinical information was reviewed and abstracted into a standardized questionnaire by one investigator from Manaus (A.P.). Up to five clinical diagnoses previously coded in ICD-10 registered in the medical record were extracted. In this list, we assumed that diagnosis number 1 was the principal diagnosis, and the remaining diagnoses were secondary. All CoD were divided into the four major categories of diseases. Diagnostic discrepancies were evaluated using the classification of Goldman et al. [23] modified by Battle et al. [24] and as non-classifiable cases [25]. Major discrepancies were classified as class I or class II. Minor discrepancies were classified as classes III and IV, as previously described [8]. Correctly diagnosed patients were classified as class V. Class VI were non-classifiable cases.

Statistical methods

The concordance between the MIA and the gold standard diagnosis (CDA) as well as the concordance between the clinical and the gold standard diagnosis were assessed by the Kappa statistic and interpreted as suggested by Landis and Koch [26]. The diagnostic accuracy of the MIA to identify the categories was evaluated as sensitivity, specificity, positive and negative predictive values and total percentage of cases correctly classified.

Additionally, the coincidence between the MIA and the CDA diagnoses, as well as the coincidence between the clinical and the CDA diagnoses for each case were assessed by comparing ICD-10 codes. The ICD-10 classifies diagnoses into nested classes of different hierarchical levels, where diseases or conditions are organized in chapters, blocks, and three character categories [21, 22]. Thus, a coincidence was classified as perfect when the ICD-10 codes were identical in chapter, block and three-character categories [21]. Coincidence was classified as moderate when the codes were within the same chapter and block, but there was a discrepancy in the three-character category and as low when the codes were within the same chapter, but there was a discrepancy in the block and three-character categories. When the MIA and the gold standard diagnoses were in a different chapter, the coincidence in diagnosis was classified as “none”.

Statistical analyses were performed using the Stata Software (Version 15, StataCorp 2017, College Station, TX, USA).

Results

General characteristics of the series

Coupled MIA and CDA were performed to 61 patients (39 males [64%] and 22 females [36%]). Fifty-nine of the patients were adults; two of them were maternal deaths (one woman who died during pregnancy and another who died during the puerperal period). The series included two children (a female and a male, both 13 years old). The median age of the overall group was 34.8 (range 13.9 to 81.5 years).

Gold standard (CDA) diagnosis of CoD

A final CoD was identified in the CDA for all cases. The CDA classified 44/61 (72%) deaths as infectious (28 disseminated, eight pulmonary, seven CNS, and one liver infection). Eleven deaths (18%) were caused by malignancies (five liver cell carcinomas, six other malignancies), and 6/61 deaths (10%) were caused by other diseases. None of the maternal deaths was of a direct obstetric cause (one pulmonary thromboembolism complicating sickle cell anaemia and a liver cell carcinoma).

An underlying CoD was identified in the CDA in 51/61 of the cases (84%). Underlying diseases included HIV infection in 37 patients (61%). All of them tested positive for HIV antibodies (all being HIV-1). Hepatitis B virus (HBV) infection was identified in seven cases, three of them with an HDV (Hepatitis D virus)-HBV co-infection. In three patients, cirrhosis without aetiology was identified. One patient had sickle cell anaemia, one HTLV (Human T-lymphotropic virus) I-II infection and one systemic lupus erythematosus with glomerulonephritis.

Concordance in disease categorization between the MIA and the CDA and accuracy of the MIA

A final cause of death was identified in the MIA in all cases. The MIA categorization of diseases agreed with the gold standard in 55/61 (90%) of the cases and showed a substantial concordance with the CDA categorization (Kappa = 0.780, 95% CI 0.608–0.946). Concordance in all categories was high, with a 100% (6/6) for other diseases, 93% (41/44) for infections and 73% (8/11) for the malignancies. From the discrepant cases, three out of 44 infections were classified as other diseases, and three out of eight malignancies were classified as infections.

Table 1 shows the sensitivity, specificity, the positive and negative predictive values for the major diagnostic categories, as well as the accuracy of the MIA diagnoses. Sensitivity and overall accuracy of the MIA were high for all categories, over 70% and 90%, respectively.

Table 1 Sensitivity, specificity, positive and negative predictive value (PPV and NPV) and accuracy of the MIA for the different diagnostic categories. Figures are percentages and 95% confidence intervals

Cause of death	Number	Sensitivity	Specificity	PPV	NPV	Correctly classified
Infectious diseases	44	93 (85,99)	82 (57,96)	93 (82,99)	82 (57,96)	90 (80,97)
Malignant tumours	11	73 (39,94)	100 (93,100)	100 (63,100)	94 (84,99)	95 (86,99)
Other diseases	6	100 (54,100)	95 (85,100)	67 (30,93)	100 (93,100)	95 (86,99)

Kappa (Std. Err.) 0.777—Substantial. 95% CI 0.608–0.946

MIA minimally invasive autopsy

Coincidence between the MIA and the gold standard diagnoses

For the cases with no discrepancies ($n = 55$) between the MIA and the CDA diagnoses, we performed an additional analysis to evaluate the degree of coincidence (from perfect to none) between the specific ICD-10 diagnoses. Table 2 summarizes the coincidence in ICD-10 coding, in terms of identical chapter and block, according to disease category. The coincidence was perfect (i.e. the same specific disease, diagnosed as the CoD) in 47 of the 55 cases (85%). For the disease categories, this perfect level of coincidence was 67% for other diseases, being higher for infectious diseases and malignant tumours (over 85%, each). In the seven cases with moderate to low coincidence, the MIA failed to determine the organ or the microorganism (five cases of infectious diseases), the location of the carcinoma (one case) or the precise cardiovascular disease leading to death (one case of other diseases). In one case, the coincidence was considered none and included a pulmonary thromboembolism complicating a sickle cell anaemia crisis in which the MIA identified only a pulmonary infarct.

Other significant diseases or co-infections were identified in 33/61 (54%) cases of the MIA and in 42/61 (69%) cases of the CDA, being coincident between the MIA and the CDA in 28 cases (46%).

Table S1 summarizes the CDA and MIA CoD, the underlying conditions and any other significant conditions identified at the CDA and the MIA for each individual patient, as

well as the ICD-10 code for each diagnosis and coincidence between the MIA and the gold standard diagnosis.

Aetiological agents and contribution of pathological and microbiological findings in infectious CoD

In 40/44 (91%) of the infection-related deaths, the aetiological agent was identified in the CDA. In the group of disseminated infections, seven patients had a millitary tuberculosis (6/7 HIV-positive), six had a disseminated histoplasmosis (all of them HIV-positive), five had a bacterial sepsis (three *Neisseria meningitidis*, two *Streptococcus pneumoniae* [one of the latter HIV-positive]), three had a disseminated cryptococcosis, three had a toxoplasmosis and two patients disseminated cytomegalovirus disease (all of them HIV-positive). Finally, one patient had disseminated leishmaniasis and one histological findings of haemorrhagic viral disease, although the agent was not identified after testing for dengue, yellow fever, leptospirosis and hantaviruses. The pulmonary infections included one tuberculosis, one pneumocystosis and two cases of cytomegaloviral pneumonia (all in HIV-positive patients); we also diagnosed two patients with pneumonia and one case with organizing pneumonia, but no agent was identified. The CNS infections included three toxoplasmosis, two cryptococcosis (all in HIV-positive patients) and two bacterial meningitis (one caused by *N. meningitidis* and one by *Klebsiella pneumoniae*).

Table 2 Diagnostic coincidence within the 55 cases with concordant diagnosis between the MIA and the CDA

Disease group	Coincidence in diagnosis (MIA vs. CDA)					
	Perfect/almost perfect		Moderate or low		None	
	<i>n</i>	% (95% CI)	<i>N</i>	% (95% CI)	<i>n</i>	% (95% CI)
Overall ($n = 55$)	48	87 (66–88)	6	11 (4–20)	1*	4 (0–8)
Infectious diseases ($n = 41$)	37	90 (47–72)	4	10 (2–16)	0	0 (0–6)**
Malignant tumours ($n = 8$)	7	87 (5–22)	1	12 (0–9)	0	0 (0–6)**
Other diseases ($n = 6$)	4	67 (2–16)	1	17 (0–9)	1	17 (0–9)

MIA minimally invasive autopsy, CDA complete diagnostic autopsy, CI confidence interval

*The case in which the coincidence was considered “none” is a sickle cell anaemia crisis that the MIA diagnosed as a pulmonary infarct. **One-sided, 97.5% Confidence interval

The same microorganism identified in the gold standard CDA was identified in the MIA in 35 out of the 40 cases (87%). Table 3 shows the aetiological agents identified in the CDA and in the MIA.

Among the 44 infection-related deaths, the pathological findings alone were sufficient for the cause of death diagnosis in 12 cases (27%) of the MIA and in 5 cases (11%) of the CDA. In 23 cases (52%) of the MIA and in 39 (89%) cases of the CDA, the pathological and the microbiological findings contributed equally, with microbiology providing information on the aetiological agent. Finally, in 9 cases of the MIA (21%), the pathological findings were non-conclusive and the diagnosis was based on the microbiological analysis.

Clinico-pathological discrepancies

The clinical categorization of disease showed a fair concordance with the CDA categorization (Kappa = 0.311, 95% CI 0.071–0.552). The sensitivity of the clinical diagnosis was 93% for infectious diseases (95% CI 81–93%), 67% for other diseases (95% CI 22–96%) and 0% for malignant tumours (95% CI 0–28%).

Overall, a diagnostic discrepancy was determined in 31/61 (51%) of the cases. A major diagnostic discrepancy was detected in 30 (49%) of deaths: 25 (41%) were classified as class I, and five (8%) as class II. A minor diagnostic discrepancy (class III) was identified in one case. In 30 cases (49%), there was complete agreement between the clinical and the autopsy diagnoses (class V). Twenty-one of the 30 major discordances (70%), occurred in infections, six (20%) in malignancies and three (10%) in other diseases. No statistical differences in terms of percentage of major errors were observed between the main diagnostic categories ($p = 0.142$). No association was observed between demographic data, clinical symptoms at admission and biochemical parameters and type of clinico-pathological discrepancies.

Discussion

To our knowledge, this is the first study reporting the validity of a standardized MIA for CoD determination and including the evaluation of the clinico-pathological discrepancies in the Brazilian Amazon. The validation study shows a substantial degree of concordance (90%; kappa value of 0.78) between the MIA and the gold standard diagnoses. The concordance was remarkably high in all disease categories, particularly for infectious diseases. These results are consistent with the reported concordance in a series of adults in Mozambique [11] and show that the MIA can be an adequate alternative in LMIC settings, where mortality statistics are poor.

Infectious diseases, representing over 70% of all deaths, and HIV infection (61% of all cases) were as prevalent as in

our previous study in Mozambique [11]. These infections include endemic diseases such as histoplasmosis and leishmaniasis, as well as microorganisms such as *N. meningitidis* that were not identified in previous validation studies [11, 13, 14]. Importantly, in 87% of the cases, the aetiological microorganism was identified in the MIA. Interestingly, all five missed aetiological agents, not identified at MIA and detected with molecular methods in the CDA-obtained tissues, were CNS infections. In three cases, this was due to the absence of meningeal membranes in the MIA sample (two meningitis), and in two cases, the histological lesion and the microorganism were absent in MIA sample (two toxoplasmosis). These findings also indicate that the CSF collected, during MIA, cannot be sufficient on its own to identify infectious agent affecting the CNS. Future MIA protocols may benefit from an increase in the number of CNS samples in order to increase the yield of the microbiological and histological results in meningeal infections.

Similar to other settings, *M. tuberculosis* was the most frequent fatal opportunistic infection among HIV-positive patients in Manaus. *Cryptococcus* spp. was also a frequent cause of death [11, 27]. In keeping with other studies in Latin America [28], histoplasmosis, an endemic fungal infection, was the second most frequent infectious disease identified as CoD in the HIV-positive patients from our series. In a previous autopsy study conducted in the same setting and including HIV patients from 1996 to 2003, tuberculosis (28%) and histoplasmosis (17%) were also the two most frequent causes of death [29]. These results are similar to other studies in Latin America, including Brazil, reporting high incidence and mortality of histoplasmosis especially in HIV-positive patients [30–32]. The high frequency of histoplasmosis in this area indicates that this infection needs to be considered as part of the differential diagnosis early during clinical management of HIV-positive patients.

Bacterial pneumonia was an infrequent CoD in the present series in HIV-positive patients, which contrasts with previous reports [29, 33]. These results may reflect an improvement in the management of bacterial infections in HIV-positive patients [29]. Finally, blood samples obtained during MIA, allowed us to identify all HBV infections (seven cases), which in three cases had an associated HDV co-infection. In addition, an HTLV I-II co-infection was also identified.

Hepatocellular carcinoma was the most frequent malignancy in this series; all were diagnosed in HIV negative patients. Four out of the five hepatocellular carcinomas identified were associated with HBV infection. Thus, although HCV infection is now the most frequent risk factor associated with HCC in South America, including Brazil [34, 35], HBV infection remains an important risk factor for HCC in some regions, including the study area. The high accuracy of MIA to detect malignant tumours is consistent with previous data [11]. However, in three patients, a malignant tumour identified in

Table 3 List of aetiological agents identified in the complete diagnostic autopsy, the minimally invasive autopsy and in both methods, expressed in number of cases

Aetiological agents	Complete diagnostic autopsy (CDA, gold standard)	Minimally invasive autopsy (MIA)	Microorganism identified by both methods (MIA and CDA)
Disseminated infections	27	27	27
<i>Mycobacterium tuberculosis</i>	7	7	7
<i>Histoplasma capsulatum</i>	6	6	6
<i>Cryptococcus</i> spp.	3	3	3
<i>Toxoplasma gondii</i>	3	3	3
<i>Neisseria meningitidis</i>	3	3	3
<i>Cytomegalovirus</i>	2	2	2
<i>Streptococcus pneumoniae</i>	2	2	2
<i>Leishmania</i> spp.	1	1	1
Pulmonary infections	5	5	5
Cytomegalovirus	2	2	2
<i>Pneumocystis jirovecii</i>	1	1	1
<i>Pseudomonas aeruginosa</i>	1	1	1
<i>Mycobacterium tuberculosis</i>	1	1	1
Central nervous system infections	7	2	2
<i>Toxoplasma gondii</i>	3	1	1
<i>Cryptococcus</i> spp.	2	0	0
<i>Neisseria meningitidis</i>	1	1	1
<i>Klebsiella pneumoniae</i>	1	0	0
Other infections	1	1	1
Viral hepatitis A	1	1	1
Total	40	35	35

The entries that were marked in bold are the main groups of different diagnosis

*No agent was identified in three pulmonary infections and one disseminated infection

the CDA was not diagnosed in the MIA. All these tumours missed at MIA were localized tumours, being out of the target regions of the MIA (hepatocarcinoma, one large B cell lymphoma and one gastric adenocarcinoma).

Clinico-pathological discrepancies were identified in 51% of the cases (31/61), with most of the discrepancies being major errors (30 cases; 49% of the overall series). Importantly, in most patients (41%), a change in the clinical management could have significantly modified the prognosis (type I errors). The percentage of discrepancies observed in this series is similar to the data of tertiary hospital of Mozambique and is higher than in most studies based on unselected hospital patients [18, 23–25].

The main limitation of our study is that it was conducted in a referral tertiary care centre focused on infectious diseases, in a cohort of cases with a high HIV prevalence, not representative of the population. This could limit the extrapolation of the findings to other health facilities and to high-income countries, where HIV and infections may be less prevalent and cardiovascular diseases and malignant neoplasms are frequent causes of death. However, the

present study was conducted in a completely different geographic area compared to our previous studies, conducted in sub-Saharan Africa [11, 12, 14], indicating that MIA may provide robust mortality data irrespectively of the region.

In conclusion, in this series of adult deaths from the Brazilian Amazon, the MIA showed a substantial performance for CoD determination. The results confirm that the MIA is a valid tool, comparable to the gold standard methodology, particularly for infectious diseases, and that it can be reliably considered an adequate proxy for the CDA for CoD surveillance and quality improvement of clinical practice. The high accuracy of the MIA to detect infectious diseases indicates that the procedure has a potential use to detect infectious diseases outbreaks and emerging diseases in sentinel sites. Major clinico-pathological discrepancies remain significantly high (41%), even in a referral hospital with adequate diagnostic resources and specialized physicians, as to justify the need for post-mortem procedures, which may help to improve clinical practice in LMIC.

Acknowledgements We would like to express our gratitude to the families of the deceased patients included in this study. The authors are thankful to all the members of the pathology department of the *Fundação de Medicina Tropical Dr. Heitor Vieira Dourado* (FMT-HVD).

Conflict of interest The authors declare that there are no competing interests.

Author's contributions Juan Carlos Hurtado, Natalia Rakislova, Rosauro Varo, Mireia Navarro, Isaac Casas, and Wuelton M. Monteiro collected, interpreted the data and revised the manuscript.

Ariadna Sanz was responsible of the data interpretation and revision of manuscript.

Llorenç Quintó performed the statistical analysis and reviewed the manuscript.

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All authors gave final approval for publication.

Jaume Ordi takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

Funding The CaDMIA research project (Validation of the minimally invasive autopsy tool for cause of death investigation in developing countries) was funded by the Bill & Melinda Gates Foundation (Global Health grant numbers OPP2068633; QB) (<http://www.gatesfoundation.org>) and by the Spanish Instituto de Salud Carlos III (FIS, PI23/00868; CM) (<https://portalfis.isciii.es>). Data analysis has been supported by the CaDMIA plus research project, funded by the Bill & Melinda Gates Foundation (Global health grant numbers OPP2239002; JO) (<http://www.gatesfoundation.org>) and the Spanish Instituto de Salud Carlos III (Acciones CIBER; CM) (<http://www.ciberisciii.es/>). ISGlobal is included in the CERCA Programme/Generalitat de Catalunya.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study received the approval of the Clinical Research Ethics Committee of the Hospital Clinic of Barcelona (File 3024/9688) and the local (Manaus, Amazonas state) and National (Brazil) Bioethics Committees (CAAE 28905514.0.0000.0005/2014).

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